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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/716,283 | 11/18/2003 | David P. Jacobus | JACB-0053 | 6080 |

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Walter C. Frank
WOODCOCK WASHBURN LLP
46th Floor
One Liberty Place
Philadelphia, PA 19103

| EXAMINER | |
|---|---|
| BALASUBRAMANIAN, VENKATARAMAN | |
| **ART UNIT** | **PAPER NUMBER** |
| 1624 | |

DATE MAILED: 11/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| **Advisory Action Before the Filing of an Appeal Brief** | **Application No.** 10/716,283 | **Applicant(s)** JACOBUS ET AL. | |
|---|---|---|---|
| | **Examiner** Venkataraman Balasubramanian | **Art Unit** 1624 | |

***--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --***

THE REPLY FILED 25 October 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: *1,3-90 and 99*.
   Claim(s) objected to: _____.
   Claim(s) rejected: *100*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☐ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☒ Other: See attached Advisory Action.

Venkataraman Balasubramanian

Venkataraman Balasubramanian
Primary Examiner
Art Unit: 1624 11/8/06

## ADVISORY ACTION

The applicants' response, which included amendment to claims, filed 10/25/2006 under 37 CFR 1.116 in reply to the final rejection has been considered but is not deemed to place the application in condition for allowance for the following reasons.

The following rejection, made in the previous office action, remains. Effort was made the to resolve the issue of "preventing infection" caused by infection of Plasmodium Sp. embraced in claim 100 with counselor Walter Frank on 11/8/2006 but did not result in any agreement. Hence, the rejection is maintained.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 100 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating, as implied in claim 99, of specific infection of Plasmodium Sp., Mycobacterium Sp. , Toxoplasma gondii and Pneumocystis carnii, does not reasonably provide enablement for preventing infection of Plasmodium Sp. As implicitly embraced in claim 100. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Following apply.

The instant claim 100 is to "protecting a patient susceptible to infection caused by exposure to an organism selected from Plasmodium Sp. , Mycobacterium Sp. ,

Toxoplasma gondii and Pneumocystis carnii," which means prophylactic use of the compound of claim 1. The instant compounds are disclosed to have bacterial and parasitic growth inhibition activity and it is recited that the instant compounds are therefore useful in preventing, besides treating, Plasmodium Sp. , Mycobacterium Sp. , Toxoplasma gondii and Pneumocystis carnii, for which applicants provide no competent evidence. It appears that the applicants are asserting that the embraced compounds because of their mode action as bacterial and parasitic growth inhibitor that would be useful for preventing said diseases. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for preventing these diseases for the intended host. The prophylactic use is to prevent.

To "prevent" actually means to anticipate or counter in advance, to keep from happening etc. (as per Websters II Dictionary) and there is no disclosure as to how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "prevention" effect. There is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the bacterial and parasitic infections.

That a single class of compounds can be used to prevent asthma and chronic obstructive pulmonary disease in general embraced in the claims is an incredible finding for which applicants have not provided supporting evidence. Moreover , diseases like malaria, tuberculosis are very difficult to treat and despite the fact that there are many bacterial and malarial drugs, none of them have found to prevent the said diseases.

Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method of preventing solely based on the inhibitory activity disclosed for the compounds. Prior art search in this area only lend support for treating the said diseases not preventing these diseases. See Snyder et al., J. Med. Liban 48(4): 208-214, 2000 (PubMed Abstract provided), wherein with regards to antibacterial therapies, it is stated that " common bacteria whose susceptibility to antimicrobials is no longer predictable". Note also that despite the fact there are several commercial antibacterial agents are available, it is still difficult to even treat let alone prevent several pathogens such as those cause leprosy, TB, malaria, meningitis, sexually transmitted infections, anthrax etc.

In evaluating the enablement question, several factors are to be considered. Note In re Wands, 8 USPQ2d 1400 and Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in preventing Plasmodium Sp. , Mycobacterium Sp. , Toxoplasma gondii and Pneumocystis carnii, that require growth inhibitory activity.

2) The state of the prior art: A recent publication expressed that the PDE inhibition effects are unpredictable and are still exploratory. See Synder cited above.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for preventing Plasmodium Sp. , Mycobacterium Sp. , Toxoplasma gondii and Pneumocystis carnii. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show Plasmodium Sp., and the state of the art is that the effects of antibacterial are unpredictable.

6) The breadth of the claims: The instant claim embrace a method of protecting a patient susceptible to infection caused by exposure to infection of Plasmodium Sp.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant

case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of enzyme-inhibitor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was 'filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

This rejection is same as made in the previous office action. Applicants' argument to overcome this rejection was not persuasive.

First of all, specification has not support for preventing the infection caused by the infection of Plasmodium Sp.

Secondly, applicants arguments are focused on preventing malaria which is not same as preventing the infection cause by infection of Plasmodium Sp.

Thirdly applicants have not shown who are the patients susceptible to the infection and what way one trained the art would establish this population. As it stands every one is susceptible to infection by microorganisms.

Applicants have argued that chemoprophylaxis may refer to absolute prevention of infection but the discussion thereof clearly includes infection of the patient with various stages of parasites. See page 21 second paragraph of the response.. Thus there is no absolute prevention of infection but treating the patient to reduce the level of infection.

This is clearly evident in claim 99 which recites "a method of reducing in a patient the level of infection caused by an organism...".

As for applicants' referral to Physician' Desk Reference, applicants have not provided the appropriate pages for review. In addition, the said Desk reference is intended for drugs used to treat and their indications for diseases.

As for applicants' assertion that the compounds of the invention showed activity in the mouse malarial model, the issue is whether the instant compound prevented the infection not whether the compounds show efficacy in the treatment protocol. As seen in page 42 of specification, the data provided is indicative of the effect of treating not an evidence of preventing the infection.

As for applicants' argument that people who travel take known antimalarial drugs, it is noted that the there is no evidence presented that they are not infected with Plasmodium Sp. Again reducing the level of infection is not considered as prevention. For most part, one trained in the art would be aware of the fact the malaria is still prevalent and that there is no prevention of malaria and that the parasites which cause malaria develop drug resistance. Thus, it stands to reasoning that if such a parasite

develops drug resistance, which of course currently a problem in chemotherapy of malaria, then even treating would become infective.

Based on these considerations, the rejection is deemed as proper and is maintained.

***Allowable Subject Matter***

Claims 1, 3-90 and 99 would be allowable barring finding of any prior art in a subsequent search.

**Conclusion**

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you

have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

Venkataraman Balasubramanian

11/8/2006